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(54) **TISSUE INJECTABLE COMPOSITION**

IN KÖRPERGEWEBE INJIZIERBARE ZUSAMMENSETZUNGEN

COMPOSITION INJECTABLE DANS LES TISSUS

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Description

[0001] The present invention concerns an injectable, biocompatible composition for tissue augmentation according to the precharacterizing portion of claim 1.

[0002] This invention relates to an injectable composition of physiologically compatible and appropriately sized particles carried in a lubricative, biologically compatible fluid or gel. The composition is formulated to be delivered into the body to a tissue site through a small-bore instrument to strengthen, bulk-up and otherwise augment the tissue site and surrounding area.

[0003] The percutaneous injection of substances into tissues to augment, support, or reconfigure anatomic structure has been the subject of significant research and product development and is well known in the art. See, for example, US-A- 4,803,075 and 5,204,382 to Wallace et al and 5,258,028 to Ersek et al. Procedures have been described in the medical literature for correction of dermatological, otolaryngological problems and for treatment of urological disorders, e.g., Walker et al., "Injectable Bioglass as a Potential Substitute for Injectable Polytetrafluoroethylene," J. Urol., 148:645-7, 1992 and the references cited therein.

[0004] Urinary incontinence and vesicourethral reflux are urological disorders that have responded to treatments with augumentive materials. US-A- 5,007,940; 5,158,573; and 5,116,387 to Berg disclose biocompatible compositions comprising discrete, polymeric and silicone rubber bodies injectable into urethral tissue for the purpose of treatment of urinary incontinence by tissue bulking. The most serious adverse effect that may occur from therapies of this type relates to the migration of the solid materials from the original site of placement and into repository sites in various body organs. An important factor in assuring nonmigration is the administration of properly sized particles. If the particle is too small, it is likely to enter the microvasculature system and travel until it reaches a site of greater constriction. Target organs for reposition include the lungs, liver, spleen, brain, kidney, and lymph nodes.

[0005] The primary focus of this invention has been directed toward the development of biocompatible, nonmigratory particles that are effectively delivered to the desired tissue site in a lubricative, biocompatible fluid or gel carrier. The preferred carrier shall not cause any deleterious effects at or near the site of particle delivery and will be removed from the site by normal biological or biochemical processes such as excretion or metabolic breakdown.

[0006] The injectable, biocompatible composition of the present invention is defined in claim 1. Preferred embodiments are shown in the sub-claims.

[0007] In accordance with the present invention there is provided an injectable, biocompatible composition comprised of a plurality of discrete, physiologically compatible, carbon-coated particles of a predetermined size range and a lubricative fluid or gel in which the particles are carried. The carrier is a biologically compatible solution, suspension or gel. The particles range in size from 100 µm (microns) to 1,000 µm (microns) in transverse, cross-sectional dimension.

[0008] The composition is designed to be delivered into the body through a small-bore needle, cannula, or catheter and to a tissue site for the purpose of augmenting the tissue site and surrounding area, thereby correcting a defect, filling a void or strengthening the support structures of the tissue.

[0009] The composition is comprised of two components.

[0010] The first is a plurality of carbon-coated particles ranging in size as microbeads or microparticles from a minimum of 100 µm (microns) to a maximum of 1,000 µm (microns). The particles are subjected to a coating process in which carbon is deposited as a thin coating or film on an appropriate, particulate substrate, thereby creating a particle that has a highly biocompatible surface. A hard, metallic substance capable of withstanding the high temperature conditions of the coating process for low temperature isotropic (LTI), pyrolytic carbon is the preferred particulate material. Zirconium oxide has been found to be especially suitable as such a substrate. However, other metallic substrates, including but not limited to medical grade (504) stainless steel, titanium and titanium alloys are also quite acceptable as the substrate material. Gold and silver, which have lower melting temperatures, may be utilized as the particulate substrate in the vacuum vapor deposition process for ultra low temperature isotropic carbon.

[0011] The second component acts as the lubricative carrier for the carbon-coated particles and in the preferred embodiment is comprised of a suspension, solution, or other biologically compatible fluid or a gel. Examples of biologically compatible carriers include but are not limited to beta-glucan, hyaluronic acid and derivatives thereof, polyvinyl pyrrolidone or a hydrogel derivative thereof, dextrans or a hydrogel derivative thereof, glycerol, polyethylene glycol, succinaylated collagen, liquid collagen, and other polysaccharides or biocompatible polymers either singly or in combinations with one or more of the above-referenced solutions. The preferred carrier must be capable of being formulated into a viscous fluid or into a self-supporting gel. For purposes of this invention, the carrier shall be of sufficient viscosity to suspend the particles.

[0012] The composition consists of an injectable composition that is a combination of a plurality of small, smooth-surfaced particles that are carried in a lubricative fluid or gel that is preferably comprised of a biologically compatible, lubricous solution, suspension, other fluid or gel.

[0013] The particles comprise microbeads or microparticles of a hard, material serving as a substrate and having a thin coating or film of biocompatible, isotropic carbon deposited on their surfaces. The substrate material is preferably radiopaque. Different types of carbon

coating processes may be utilized, with the particulate substrate being a metallic substance selected for compatibility with the coating process.

[0014] Low temperature isotropic (LTI) pyrolytic carbon is a preferred carbon coating. Pyrolytic derives from the term pyrolysis, which is a thermal decomposition of hydrocarbons to produce a carbon material. Pyrolytic carbon is produced in a process in which hydrocarbons and alloying gases are decomposed in a fluidized or floating bed. Inert gas flow is used to float the bed and the substrate particles. The hydrocarbon pyrolysis results in high carbon, low hydrogen content spheres, which deposit as solids upon the substrate in the fluidized bed. As they deposit at temperatures of 1200-1500°C, the spheres may coalesce, deform, or grow due to atom movement, resulting in a high density coating. A hard, metallic substance capable of withstanding the high temperature conditions of the coating process is the preferred particulate material. Zirconium oxide has been found to be especially suitable as such a substrate. However, other metallic substrates, including but not limited to medical grade stainless steel, titanium and titanium alloys and all oxide derivatives of each, are also quite acceptable as the substrate material.

[0015] Ultra-low-temperature isotropic carbon may be applied as a coating in vacuum vapor deposition processes. Carbon can be deposited effectively utilizing ion beams generated from the disassociation of CO_2, reactive disassociation in vacuum of a hydrocarbon as a result of a glow discharge, sublimation of a solid graphite source or cathode sputtering of a graphite source, as examples of such processes. Gold has been found to be suitable as a substrate material ideal for vacuum vapor deposited carbon, however, other substrates, including but not limited to nickel, silver, stainless steel, or titanium are also quite acceptable as the substrate material.

[0016] Vitreous or glass carbons may also serve as the coating material. These are also isotropic, monolithic carbons, which are formed by pyrolysis of carbonaceous preforms, during which gaseous pyrolysis products diffuse through the shape and are liberated.

[0017] The atomic structure of either pyrolitic LTI carbon or vitreous carbon is similar to graphite, the common form of carbon, but the alignment between hexagonal planes of atoms is not as well ordered. Pyrolitic carbon is characterized by a more chaotic atomic structure with warped hexagonal planes, missing atoms and generally a more turbostatic appearance. This results in better bonding between layer planes.

[0018] The coating process is applied to small substrate particles to produce final, rounded particles that have a smooth carbon-coated surface in the form of a thin, black film. The resulting smooth surface on the particles enhances their passage through an injection needle, cannula or catheter and into body tissue. The high strength, resistance to breakdown or corrosion, and durability of the carbon coating insures the effective, long term functioning of the particles in tissue augmentation at the injection site. The established biocompatibility of pyrolytic carbon renders it particularly suitable for the anticipated body tissue applications. After the carbon coating has been applied, the particles are subjected to a cleaning and sieving process to remove contaminants and to separate out particles of a size less than or greater than the desired size range. The particles may range in size from 100 μm (microns) to 1,000 μm (microns in average, transverse cross-sectional dimension, and a preferred size range is between 200 and 500 μm (microns). That size avoids particle migration from the injection site and facilitates injection through a small bore instrument. The substrate panicles are initially milled, extruded or otherwise formed to the desired particle size, in a substantially rounded shape prior to being subjected to the coating process. The particles are randomly shaped and rounded, ranging from oblong to generally spherical. The sieving process is such that the minimum particle dimension will pass through a U.S. No. 18 Screen Mesh (1000 μm (microns) grid size opening) but will not pass through a U.S. No. 140 Screen Mesh (106 μm (microns) grid size). That minimum dimension will be the transverse, cross-sectional dimension on oblong or elongated particles, with that dimension coinciding with the particle diameter on generally spherical particles.

[0019] The carrier is preferably an aqueous suspension or solution, other fluid or gel of polymeric chains of B-D-glucose, commonly referred to as B-glucan. The glucose units are linked to each other at the 1-3, 1-4, or 1-6 positions and form polymeric chains ranging to several thousand daltons in weight.

[0020] B-glucan is a naturally occurring constituent of cell walk in essentially all living systems including plants, yeast, bacteria, and mammalian systems. Its effects and modulating actions on living systems have been studied extensively (see Abel, G., and Czop, J. K., "Stimulation of Human Monocyte B-Glucan Receptors by Glucan Particles Induces Production of TNFϑ and 1L-B" Int. J. Immunopharmacol., 14(8):1363-1373, 1992 and references included therein). B-glucan, when administered in experimental studies, elicits and augments host defense mechanisms including the steps required to promote healing by first intent, thereby stimulating the reparative processes in the host system. B-glucan is rapidly removed from tissue sites through macrophagic phagocytosis or by enzymatic destruction by serous enzymes. The rapid destruction or removal of B-glucan, as well as its available viscosity and lubricous nature, makes it an optimum carrier for the particles.

[0021] Aqueous solutions, suspensions, fluids, or gels of B-glucan can be produced that have favorable physical characteristics as a carrier for carbon-coated particles. The viscosity can vary from a thin liquid to a firm, self-supporting gel. Irrespective of viscosity, the B-glucan has excellent lubricity, thereby creating a parti-

cle-carrier composition which is easily administered by delivery to a predetermined body site through a small bore needle, cannula, or catheter. The carrier will be of sufficient viscosity to assure that the carbon-coated particles remain suspended therein. Other examples of appropriate carriers include hyaluronic acid, polyvinyl pyrrolidone or a hydrogel derivative thereof, dextran or a hydrogel derivative thereof, glycerol, polyethylene glycol, succinylated collagen, liquid collagen, oil based emulsions such as corn oil or safflower, or other polysaccharides or biocompatible organic polymers either singly or in combination with one or more of the above-referenced solutions.

[0022] In use, the above-described composition will be injected in a fluid state, e.g., as a slurry, fluid suspension or emulsion, or as a gel through a syringe needle or cannula into a body tissue site. When deposited into a soft tissue site, the preferred B-glucan carrier will disperse or be destroyed as set forth above. The particles are of an optimum size which will prevent their being carried away by capillary blood flow. They will thus remain at the site and will serve to fill voids, provide additional support, or correct other soft-tissue defects. For urological applications, the composition may be injected into the tissue of the urinary tract, wherein the selected site may be, for example, the bladder neck, the urethra or urethral sphincter. The resulting bulking or augmentation of the urethral tissue will restrict the size of the urethra or urinary passage and thus assist in overcoming incontinence.

[0023] In an experimental study, a syringe was utilized to contain and inject a fluid composition comprised of:

> pyrolytic isotrapic LTI carbon-coated zirconium oxide particles in a size range from 200 to 500 μm (microns) of a total mass of 400 mg suspended in;
> B-glucan formulated as a 1% weight by weight aqueous suspension, as the carrier.

[0024] The test composition was administered by periurethral injection into dogs. Infections were performed such that the bulk of the bladder neck/periurethral tissue was increased but such that the urethral lumen diameter was not compromised. One or more injections of the test material were administered in total volumes ranging from 1.9 to 2.5 milliliters.

[0025] The study was conducted in accordance with good laboratory practices and confirmed that the handling characteristics of the test material were favorable, as the material was easily injected with minimal to moderate resistance. No evidence of migration of the implant material was noted.

Claims

1. An injectable, biocompatible composition for tissue augmentation comprising: a plurality of discrete particles in a carrier, wherein the particles are substrate particles **characterized in that** said substrate particles are provided with a carbon coating and have an average, transverse cross-sectional dimension of between 100 and 1,000 μm (microns) and the carrier is a biocompatible solution, suspension or gel of a polysaccharide or of a biocompatible organic polymer having sufficient fluidity to carry and deliver the particles, and has lubricative qualities.

2. The composition of claim 1 wherein said carbon coating is isotropic carbon.

3. The composition of claims 1 or 2 wherein said carbon in said coating is selected between low temperature isotropic (LTI), pyrolitic carbon, vitrous carbon.

4. The composition of claims 1 to 3 wherein said isotropic carbon coating is ultra low temperature isotropic carbon which is vapor deposited.

5. The composition of claims 1 to 4 wherein said substrate particles are selected from the group of a metallic substrate gold or silver, zirconium oxides, stainless steel, titanium and titanium alloys, and their oxides.

6. The composition of claim 1 wherein the polysaccharide is beta-glucan.

7. The composition of claims 1-6 wherein the carrier is a solution or suspension selected from the group comprised of hyaluronic acid, polyvinyl pyrrolidone or a hydrogel derivative thereof, dextran or a hydrogel derivative thereof, glycerol, polyethylene glycol, succinylated collagen, liquid collagen, either singly or in combination.

8. The composition of claims 1 to 7 wherein said carbon coating is a smooth surface film.

9. The composition of claims 1 to 8 wherein said substrate particles are of rounded shape and said dimension is between 200 and 500 μm (microns).

10. The composition of claim 5 wherein the substrate particles are radiopaque.

Patentansprüche

1. Einspritzbare, biokompatible für eine Gewebevergrößerung dienende Zusammensetzung, welche eine große Anzahl von diskreten Teilchen auf einem Träger aufweist und in welcher die Teilchen Substratteilchen sind, **dadurch gekennzeichnet, dass**

die Substratteilchen mit einer Beschichtung aus Kohlenstoff versehen sind und eine durchschnittliche Querschnittsgröße in dem Bereich zwischen 100 und 1.000 µm (microns=Mikrometer) aufweisen und dass der Träger eine Lösung, eine Suspension oder ein Gel von biokompatibler Natur aus einem Polysaccharid oder aus einem biokompatiblen organischen Polymer ist und eine ausreichende Fließfähigkeit besitzt, um die Teilchen zu tragen und zu liefern, und dass sie schmierende Eigenschaften besitzt.

2. Zusammensetzung gemäß Anspruch 1, bei welcher die Beschichtung aus Kohlenstoff aus einem isotropen Kohlenstoff besteht.

3. Zusammensetzung gemäß Anspruch 1 oder 2, bei welcher der Kohlenstoff in der besagten Beschichtung ausgewählt wird unter einem bei niedriger Temperatur isotropen Kohlenstoff (LTI), einem pyrolitischen Kohlenstoff, einem glasartigen Kohlenstoff.

4. Zusammensetzung gemäß den Ansprüchen 1 bis 3, bei welcher die isotrope Kohlenstoffbeschichtung aus einem bei einer äußerst niedrigen Temperatur isotropen Kohlenstoff besteht, welcher aufgedampft ist.

5. Zusammensetzung gemäß den Ansprüchen 1 bis 4, bei welcher die Substratteilchen ausgewählt werden aus der Gruppe bestehend aus einem metallischen Substrat aus Gold oder Silber, aus Zirkoniumoxiden, aus rostfreiem Stahl, aus Titan und Titanlegierungen und aus Oxiden derselben.

6. Zusammensetzung gemäß Anspruch 1, bei welcher das Polysaccharid ein beta-Glucan ist.

7. Zusammensetzung gemäß den Ansprüchen 1 bis 6, bei welcher der Träger aus einer Lösung oder aus einer Suspension besteht, welche ausgewählt wird aus der Gruppe bestehend aus Hyaluronsäure, aus Polyvinylpyrrolidon oder aus einem Hydrogelabkömmling derselben, aus Dextran oder aus einem Hydrogelabkömmling desselben, aus Glycerol, aus Polyethylenglycol, aus einem succinylierten Kollagen, aus einem flüssigen Kollagen, entweder einzeln oder in Kombination.

8. Zusammensetzung gemäß den Ansprüchen 1 bis 7, bei welcher die Beschichtung aus Kohlenstoff aus einem weichen Oberflächenfilm besteht.

9. Zusammensetzung gemäß den Ansprüchen 1 bis 8, bei welcher die Substratteilchen eine runde Form aufweisen und ihre Größe in dem Bereich zwischen 200 und 500 µm (Mikrometer) liegt.

10. Zusammensetzung gemäß den Ansprüchen 1 bis 5, bei welcher die Substratteilchen für Strahlen undurchlässig sind.

Revendications

1. Une composition injectable biocompatible pour une augmentation des tissus comprenant: une pluralité de particules discrètes dans un véhicule, où ces particules sont des particules de substrat **caractérisé en ce que** les particules de substrat sont pourvues d'un revêtement de carbone et ont une dimension en section transversale moyenne entre 100 et 1000 µm (microns) et le véhicule est une solution biocompatible, une suspension ou un gel d'un polysaccharide ou un polymère organique biocompatible ayant une fluidité suffisante pour porter et délivrer les particules, et posséder les propriétés lubrifiantes.

2. Composition selon la revendication 1 où ce revêtement de carbone est un carbone isotropique.

3. Composition selon les revendications 1 ou 2 où ce carbone dans ce revêtement est choisi parmi les carbones isotropiques à basse température (LTI), le carbone pyrolitique et le carbone vitreux.

4. Composition selon les revendications 1 ou 3 où ce revêtement de carbone isotropique est un carbone isotropique à ultra basse température qui est déposée à la vapeur.

5. Composition selon les revendications 1 ou 4 où ces particules de substrat sont choisies dans le groupe d'un substrat métallique d'or ou d'argent, d'oxyde de zirconium, d'acier inoxydable, de titane et d'alliage de titane et leurs oxydes.

6. Composition selon la revendication 1 où le polysaccharide est le béta-glucane.

7. Composition selon les revendications 1 ou 6 où le véhicule est une solution ou suspension choisie dans le groupe comprenant l'acide hyaluronique, le polyvinyl pyrrolidone ou un dérivé d'hydrogel de ceux-ci, le dextrane ou un dérivé d'hydrogel de celui-ci, glycérol, polyéthylène glycol, le collagène succinylé, le collagène liquide soit seul ou en combinaison.

8. Composition selon les revendications 1 ou 7 où ce revêtement de carbone est un film superficiel lisse.

9. Composition selon les revendications 1 ou 8 où ces particules de substrat sont de forme ronde et ces dimensions se situent entre 200 et 500 µm (mi-

crons).

10. Composition selon la revendication 1 où ces particules de substrat sont radiopaques.